REMARKS

Claims 1-22 were pending in the present application. By this Amendment, Applicants have canceled withdrawn claims 14-22, without prejudice to Applicants' right to present the subject matter of these claims in a future continuing application. Applicants have amended claims 1 and 11 to address the Examiner's objections. Applicants have added new claim 23, which recites the subject matter deleted from claim 11. Applicants also are submitting replacement Drawings for Figures 4A and 4B, the replacements showing better detail than the originally submitted Drawings. This Amendment does not introduce any new matter and thus, its entry is respectfully requested. Upon entry of the present Amendment, claims 1-13 and 23 will be pending and under examination.

The November 7, 2006 Office Action

Election/Restriction

The Examiner has reviewed Applicants' arguments made in traverse of the prior Restriction Requirement and has deemed the requirement proper and therefore final. The Examiner, however, has asserted that Applicants' election, notwithstanding the remarks in support of traversal, should be treated as an election without traverse, because, in the Examiner's opinion, the Applicants' traversal was not complete under MPEP § 818.03(a).

Applicants assert that the Examiner is unjustified in determining that the election be treated as an election without traverse. Although the Examiner may not have been persuaded by

Applicants' remarks that the restriction requirement was improper, Applicants did nevertheless present arguments in traverse of the requirement, pointing out why Applicants believed the restriction requirement was improper. (See Applicants' response filed October 3, 2005). Applicants did not simply present a "mere broad allegation that the requirement is in error" (which MPEP § 818.03(a) indicates would be a reason for treating an election as one being made without traverse). Accordingly, regardless of whether the Examiner has been persuaded by Applicants' arguments in traverse of the restriction requirement, the election in response to the Restriction Requirement was properly made <u>with traverse</u>. Applicants request that the Examiner therefore acknowledge the traversal.

<u>Drawings</u>

The Examiner indicated that Figures 4A and 4B were not of sufficient quality to permit examination, and thus needed to be replaced. The Examiner also indicated that Applicant was given a TWO MONTH time period (from November 7, 2005) to submit new drawings.

In response, Applicants are submitting herewith replacement Figures 4A and 4B, which show the drawings' details more clearly than did the original drawings. Applicants also refer to the telephone conversation held January 6, 2006 between Examiner Martin and Applicants' undersigned attorney. In the conversation, the Examiner confirmed that the corrected drawings in fact <u>do not</u> need to be submitted before the February 7, 2006 due date for reply to the other outstanding rejections. The Examiner confirmed that requiring their submission by January 7,

2006, was incorrect and that indicating that extension fees would accrue from that date was similarly incorrect. In that regard, Applicants note that two month response periods are reserved for situations in which the quality of the drawings is so poor that no meaningful examination can be carried out on the claims, which of course is not the case here, given that the Office Action also includes various substantive rejections. Accordingly, no extension fees are required to accompany the submission of the corrected drawings. Applicants respectfully request withdrawal of the objection to the drawings.

Claim objections

Claim 1 was objected to for reciting the lower case "l" as an abbreviation for "liter."

In response, Applicants have replaced the lower case "l" with a capital "L" as suggested by the Examiner. Accordingly, Applicants respectfully request reconsideration and withdrawal of the claim objection.

Examiner's rejections under 35 U.S.C. §112, second paragraph

The Examiner rejected claim 1 as allegedly being indefinite. According to the Examiner, part 1(a) of the claim is indefinite because it is unclear whether the cell or the target component is immobilized on the electrode.

In response, without conceding the correctness of the Examiner's position, but to expedite allowance of the subject application, Applicants have amended claim 1 for clarity.

Applicants believe the claim amendment fully overcomes the Examiner's concern, and thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner also indicated that claim 11 is indefinite in its recitation of "for example." In response, Applicants have amended claim 11 by removing this language and the subject matter which follows, and have added new dependent claim 23. Applicants believe the Examiner's concern has been fully overcome, and thus, Applicants respectfully request reconsideration and withdrawal of this rejection.

Examiner's rejection on double patent grounds

The Examiner rejected claims 1-12 under the judicially created doctrine of obviousness-type double patenting, in view of claims 1-28 of U.S. Patent No. 6,602,399 (Fromherz et al.). The Examiner acknowledged that the claims of the '399 patent do not specifically teach that the medium has a salt concentration of $\leq$100mmol/L, but asserted that the ordinarily skilled artisan would have been motivated to experiment with different concentrations of salt solutions in order to optimize the experimental procedure. Moreover, the Examiner noted that Applicants' claim 10 specifies application of AC or DC voltage, and that while the '399 patent does not teach what form of voltage is applied, in the Examiner's opinion, one of ordinary skill in the art would have recognized that one of these voltage forms would have been used.

In response, Applicants respectfully traverse the Examiner's rejection. Fromherz et al. refers to a bioelectronic device. The device comprises a cell having an ion channel/receptor

system which is responsive to changes concerning an ionic flow across the cell membrane. Further, the cell is associated with an extracellular potential-sensitive electrode. A change of the ionic flow across the cell membrane comprises the generation of a measurable signal at this electrode. According to the knowledge of a person skilled in the art, different ion concentrations, in particular sodium and potassium ion concentrations, within and outside the cell are a prerequisite for generating such an ionic flow and/or a measurable electric signal, respectively. Different ion or salt concentrations are typically present if a cell is in an electrophysiological solution. As it is known in the art, such electrophysiological solutions contain potassium or sodium concentrations of about 4 mmol/L for potassium or about 145 mmol/L for sodium (see attached copy). The concentration ratio within the cell has to be reversed: potassium has about 139 mmol/L and sodium 12 mmol/L.

To the contrary, according to the present invention, the salt concentration in the extracellular medium is reduced to ≤100 mmol/L total ion concentration. Thus the extracellular medium applied does not correspond to electrophysiological conditions any more. Nevertheless, as can be seen from Figure 6 of the present invention, the behavior of the ion channels does not change due to the alternation from extracellular extrophysiological solution to the solution of the present invention. The maximum flow as well as the time-dependency remain unchanged and the cells do not suffer any observable damage (p. 10, 35 et seq.). It was not obvious in any way to a person skilled in the art that ion channels keep their activity and especially their conductivity in a non-electrophysiological solution without generation of a potassium/sodium ionic flow

between the extracellular medium and the inside of the cell. Moreover, no hint at all can be gathered from Fromherz et al. to use extracellular ion concentrations deviating from salt concentrations taught in the art.

Therefore, the present invention is based on a surprising observation and is not rendered obvious by U.S. 6,602,399. Accordingly, Applicants respectfully request reconsideration and withdrawal of the double-patenting rejection.

Examiner's rejections under 35 U.S.C. §103

The Examiner rejected claims 1-12 under 35 U.S.C. §103 as being obvious over Fromherz et al. (WO/2001/070002) and Fromherz et al. (U.S. 6,602,399). Moreover, claims 1-13 were rejected as being obvious over Fromherz et al. (WO/2001/07002) in view of Weaver (US2002/0168625). The Examiner's full rationale for these rejections, which relies substantially on the positions taken in connection with the above-noted double-patenting rejection, is set forth at pages 7-14 of the Office Action.

In response, Applicants respectfully traverse the Examiner's rejections. Applicants first refer to and reiterate the remarks set forth above in response to the double-patenting rejection. Moreover, Applicants note that Weaver refers to a method for activity detection and measurement in ion channels, wherein the assay buffer used is basically Cl^- free or has a maximum concentration of 2 mmol/L of Cl^-. However, while Weaver discloses low Cl^- concentrations, the applied total salt concentration is significantly higher than the maximum of

100 mmol/L of the present invention (see Table 3 of Weaver). Applicants point out that the potassium or sodium concentration of buffer, which is applied as an extracellular solution, is within the range of standard electrophysiological solutions (see above). Thus, a combination of Fromherz et al. and Weaver et al. does not lead one of ordinary skill in the art to the method of the present invention. Thus, Applicants' claimed invention is not rendered obvious by the art cited by the Examiner. Accordingly, Applicants respectfully request that Examiner reconsider and withdraw the rejections under 35 U.S.C. §103.

In view of the above remarks and amendments, Applicants believe that all of the Examiner's rejections set forth in the November 7, 2005 Office Action have been fully overcome and that the present application is in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

No fee is believed due in connection with the filing of this Amendment. If, however, any fee is deemed necessary, authorization is hereby given to charge such fee, or credit any overpayment, to Deposit Account No. 02-2135.

Respectfully submitted,

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By ______________________

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Attachments: Replacement Drawings Sheet
Copy of page from Biochemistry textbook

2923-566.response-2.wpd

Amendments to the Drawings

The attached drawing sheet includes changes to Figures 4A and 4B. The figures have been modified to better show the detail therein.

tion, we discuss both the electrical and chemical aspects of nerve impulse transmission.

Nerve Impulses Are Propagated by Action Potentials

Neurons, like other cells, generate ionic gradients across their plasma membranes through the actions of the corresponding ion-specific pumps. In particular, a (Na^+-K^+)-ATPase (Section 18-3A) pumps K^+ into and Na^+ out of the neuron to yield intracellular and extracellular concentrations of these ions similar to those listed in Table 34-6. The consequent membrane potential, $\Delta\Psi$, across a cell membrane is described by the **Goldman equation,** an extension of Eq. [18.3] that explicitly takes into account the various ions' different membrane permeabilities:

$$\Delta\Psi = \frac{RT}{\mathcal{F}} \ln \frac{\sum P_c[\mathrm{C}(out)] + \sum P_a[\mathrm{A}(in)]}{\sum P_c[\mathrm{C}(in)] + \sum P_a[\mathrm{A}(out)]} \qquad [34.9]$$

Here, C and A represent cations and anions, respectively, and, for the sake of simplicity, we have made the physiologically reasonable assumption that only monovalent ions have significant concentrations. The quantities P_c and P_a, the respective **permeability coefficients** for the various cations and anions, are indicative of how readily the corresponding ions traverse the membrane (each is equal to the corresponding ion's diffusion coefficient through the membrane divided by the membrane's thickness; Section 18-2A). Note that Eq. [34.9] reduces to Eq. [18.3] if the permeability coefficients of all mobile ions are assumed to be equal.

Applying Eq. [34.9] to the data in Table 34-6 and assuming a temperature of 25°C yields $\Delta\Psi = -83$ mV (negative inside), which is in good agreement with experimentally measured membrane potentials for mammalian cells. This value is somewhat greater than the K^+ equilibrium potential, the value of $\Delta\Psi = -91$ mV obtained assuming the membrane is permeable to only K^+ ions ($P_{Na^+} = P_{Cl^-} = 0$). The membrane potential is generated by a surprisingly small imbalance in the ionic distribution across the membrane; only ~1 ion pair/per million is separated by the membrane with the anion going to the cytoplasmic side and

TABLE 34-6. IONIC CONCENTRATIONS AND MEMBRANE PERMEABILITY COEFFICIENTS IN MAMMALS

Ion	Cell (m*M*)	Blood (m*M*)	Permeability Coefficient ($cm \cdot s^{-1}$)
K^+	139	4	5×10^{-7}
Na^+	12	145	5×10^{-9}
Cl^-	4	116	1×10^{-8}
X^{-a}	138	9	0

[a] X^- represents macromolecules that are negatively charged under physiological conditions.

Source: Darnell, J., Lodish, H., and Baltimore, D., *Molecular Cell Biology,* pp. 618 and 725, Scientific American Books (1986).

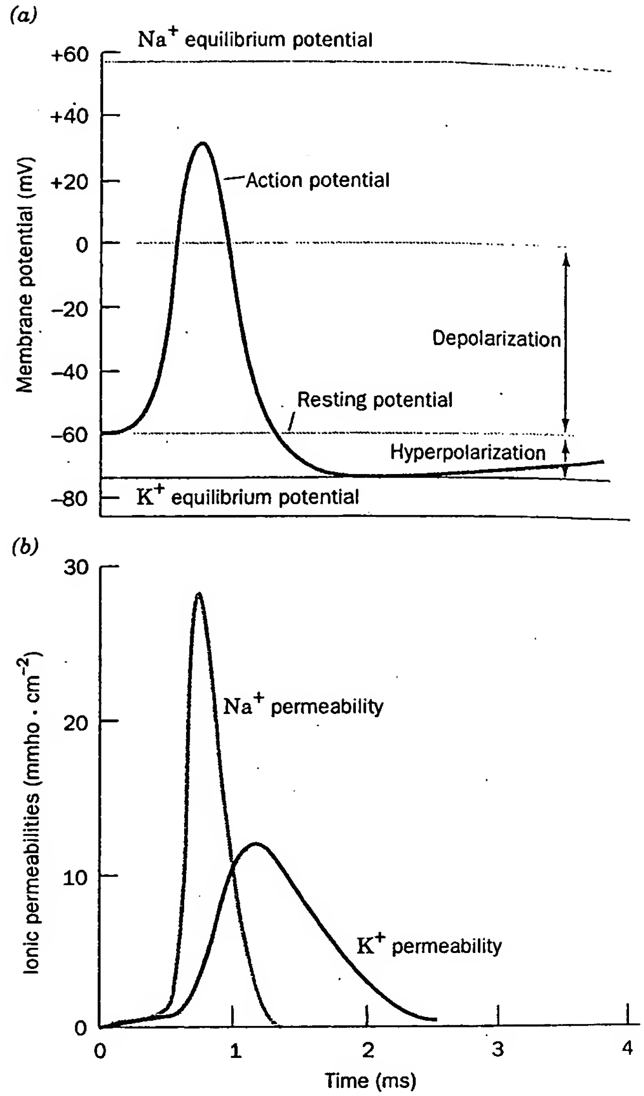

FIGURE 34-111. The time course of an action potential. (*a*) The axon membrane undergoes rapid depolarization, followed by a nearly as rapid hyperpolarization and then a slow recovery to its resting potential. (*b*) The depolarization is caused by a transient increase in Na^+ permeability (conductance), whereas the hyperpolarization results from a more prolonged increase in K^+ permeability that begins a fraction of a millisecond later. [After Hodgkin, A.L. and Huxley, A.F., *J. Physiol.* **117,** 530 (1952).]

the cation going to the external side. The resulting electric field is, nevertheless, enormous by macroscopic standards: Assuming a typical membrane thickness of 50 Å, it is nearly 170,000 $V \cdot cm^{-1}$.

A nerve impulse consists of a wave of transient membrane depolarization known as an ***action potential*** *that passes along a nerve cell.* A microelectrode implanted in an axon (the long process emanating from the nerve cell body) will record that during the first ~0.5 ms of an action potential, $\Delta\Psi$ increases from its resting potential of around −60 mV to about ~30 mV (Fig. 34-111*a*). This depolarization is

D. Voet, "Biochemistry" 2. Ed. J. Wiley u. Sons, Inc., 1995.